

REMARKS

1. Status of the pending claims.

Claims 31-42 and 57-62 have been examined in the Action. Claims 42 and 57-60, as herein amended, claims 31-41 as filed and new claim 63 are currently pending; claim 60 has been amended to overcome a formalities objection. Claims 1-30 and 43-56 are withdrawn as being drawn to a non-elected invention(s). However, Applicants wish to express their understanding that method claims 1-25 and 43-56 will be rejoined in this application once the patentability of the pending claims has been acknowledged by the Patent Office, since these claims have been amended to be dependent on claim 31. Applicants understanding is based on the Restriction Requirement, and respectfully solicit the Examiner to confirm the status of these method claims.

2. The claims as amended fulfill the requirements of 35 U.S.C. §112.

Claims 31-42 and 57-62 stand rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the invention. Applicants have overcome the asserted grounds of rejection by amendment, which are directed to the following claims and asserted deficiencies.

Claims 31-42 and 57-62 stand rejected under 35 U.S.C. §112, second paragraph for reciting “two phased tetracycline operators” as being unclear. To answer the specific question posed in the Action, the claims by this phrase recite two tetracycline operators that are positioned in phase, i.e. so that their effects on gene expression complemented, rather than opposed, each other. Applicants respectfully contend that the term “phased” would be understood by one having ordinary skill in the context of the gene expression regulatory elements to mean that the operator sequences were positioned in any way that their effect on gene expression complemented, rather than opposed, each other. The specification as filed contains explicit reference to how the term was used by Applicants, and they respectfully draw the Office’s attention to the following disclosure in their specification:

In certain embodiments, an expression vector of the present invention contains elements that allow tight regulation of gene expression. For example, the expression vector may contain one or more tetracycline repressor binding sites (tetracycline operators) in the promoter region of the vector. In a preferred embodiment, the vector comprises multiple tetracycline operators and a minimal promoter comprising a TATA sequence. Preferably, the tetracycline operators are arranged to provide tight

regulation of the promoter. One such arrangement includes two phased tetracycline operators 21 basepairs downstream from the TATA sequence and two phased tetracycline operators 11 basepairs upstream from the TATA sequence. (p.26, l. 7-16)

LNCX was modified according to Kistner to contain an array of seven cognate tetracycline operator sequences linked to a minimal CMV promoter which is itself inactive (A. Kistner, et al., Proc Natl Acad Sci USA 93, 10933-8. (1996). This arrangement was additionally modified in the LNCtX with PolyA by the insertion of two phased tetracycline operators 21 bp downstream from the TATA site and two phased tetracycline operators 11 bp upstream of the TATA sequence within the CMV promoter. This configuration positions a tight protein clamp of two dimerized TetR elements both in front of the TF-IID contact site and also exactly at the site of initiation of transcription. Moreover, binding of dimerized tetracycline repressors induces a significant kink in the double helix, further reducing the probability of fortuitous transcription. (p.34, l. 8-18)

In addition, Applicants note that their explicitly-disclosed vector, pLNCtX with PolyA, is disclosed as comprising said “two phased tetracycline operators” located 11 bp upstream and 21 bp downstream of the minimal TATA promoter sequence. Applicants thus respectfully contend that one having ordinary skill in the art would appreciate the meaning of the term “two phased tetracycline operators” and request that the Examiner withdraw this ground of rejection.

Further in this regard, the Action contains a rejection on 35 U.S.C. §112, second paragraph grounds wherein the claims are objected to for reciting that each of two tetracycline operator sequences can be 21bp downstream from the TATA sequence. Applicants first note that two tetracycline operators are not recited in the claim, but that two phased tetracycline operators, as explicated above, are what is recited. Applicants respectfully contend that one having ordinary skill in the art would understand that in the context of promoter elements the phrasing used in the claim means that the position of the elements, whether alone or in combination, is at a site 21bp downstream from the TATA sequence. This convention is adopted, *inter alia*, because it identifies the relevant topographical feature of the construct, and since otherwise the “position” of an element in a construct would comprise a range whose size depended on the size of the element. Applicants respectfully contend that the art has not adopted this way of describing expression vector topography, and that one of ordinary skill would understand that two phased tetracycline promoters are intended to be positioned at a site that is 21bp downstream from the TATA sequence. Applicants thus respectfully contend that one having ordinary skill would understand the meaning of the term

“positioned 21bp downstream of the TATA sequence,” and request that the Examiner withdraw this ground of rejection.

Yet further in this regard, the Action contains a rejection on 35 U.S.C. §112, second paragraph grounds wherein the claims are objected to for reciting that each of two tetracycline operator sequences can be 11bp upstream from the TATA sequence. Applicants respectfully contend that, for the same reasons set forth above with regard to the phrase “positioned 21bp downstream of the TATA sequence” one having ordinary skill would understand the meaning of the term “positioned 11bp upstream of the TATA sequence,” and request that the Examiner withdraw this ground of rejection.

Claim 42 stands rejected on 35 U.S.C. §112, second paragraph grounds for reciting “more than one cyclin dependent kinase.” The Action correctly points out that claim 31 recites cyclin dependent kinase *inhibitors*, and Applicants have amended claim 42 in conformity therewith. Applicants thank the Examiner for pointing out this typographical error, and respectfully ask the Examiner to withdraw this ground of rejection in light of their amendment.

Claims 57-62 stand rejected on 35 U.S.C. §112, second paragraph grounds for reciting that the claimed expression vector encodes one or a multiplicity of Cy motifs. The Action correctly states that base claim 39 recites a vector comprising a gene. However, claims 57 and 58 are directly dependent on claim 31, which describes the vector comprising the minimal promoter linked to phased tetracycline operator sequences. Applicants thus respectfully contend that claims 57 and 58 do not contravene any limitation recited in base claim 31, and request that the Examiner withdraw this ground of rejection.

Claims 57-62 stand rejected under 35 U.S.C. §112, first paragraph for containing subject matter not disclosed in the application as filed. While not conceding the correctness of the Office’s position, Applicants have cancelled claims 61 and 62 to focus their response to this ground of rejection on the claims directed to Cy motifs.

Applicants respectfully contend that their specification fulfills the requirements of 35 U.S.C. §112, first paragraph for claims 57-60 and new claim 63. Applicants respectfully bring to the Office’s attention the following portions of their specification:

Peptides that may be used include Cy region peptides. The cyclin binding Cy motif of the CIP/KIP family of CDK inhibitors (Chen et al., 1996) can interact with the cyclins independently of CDK2. The cyclin-binding motifs of p21 are required for

the optimal inhibition of cyclin-CDK kinases in vitro and for growth suppression in vivo. Peptides containing only the N-terminal or C-terminal motif of p21 partially inhibit cyclin-CDK kinase activity in vitro and DNA replication in *Xenopus* egg extracts. A Cy motif is found near the N terminus of Cdc25A that is separate from the catalytic domain (Saha et al., 1997). Mutations in this motif disrupt the association of Cdc25A with cyclin E- or cyclin A-CDK2 in vitro and in vivo and selectively interfere with the dephosphorylation of cyclin E-CDK2. A peptide based on the Cy motif of p21 competitively disrupts the association of Cdc25A with cyclin-CDKs and inhibits dephosphorylation of the kinase. p21 inhibits Cdc25A-cyclin-CDK2 association and dephosphorylation of CDK2. Conversely, Cdc25A associates with cyclin-CDK and protects it from inhibition by p21. Cdc25A also protects DNA replication in *Xenopus* egg extracts from inhibition by p21. Thus, cdc25A and p21 compete for binding with cyclin-CDK complexes. The association of cdc25A, p21, cyclins and CDKs is mediated, in part, by the Cy motif. The Cy motif sequence is found in many proteins involved in cell cycle dynamics (See Table 1). (p. 18, l. 5-23)

TABLE 1
Sequences of Cy motif in Cell Cycle Related Proteins

<u>Protein with Cy motif</u>	<u>Motif Amino Acid Sequence</u>
E2F1	KRRLDL (SEQ ID NO: 3)
E2F2	KRKLDL (SEQ ID NO: 4)
E2F3	KRRLEL (SEQ ID NO: 5)
P107Rb	KRRLFG (SEQ ID NO: 6)
P130Rb	KRRLFV (SEQ ID NO: 7)
Cdc6	GRRLVF (SEQ ID NO: 8)
Myt1	PRNLLS (SEQ ID NO: 9)
Cdc25a	RRLLLF (SEQ ID NO: 10)
P57	CRSLFG (SEQ ID NO: 11)
P27	CRNLFG (SEQ ID NO: 12)
P21 (N)	NCRRLFG (SEQ ID NO: 13)
P21 (C)	KRRLIF (SEQ ID NO: 14)

In one embodiment of the invention multimeric repeats of Cy motifs controlled by an inducible system are used to provide multiple Cy inhibitory species in order to target CDK-cyclin activity. These Cy peptides are unlikely to be targeted by the 26 S proteasome, and thus afford a more stable means of triggering cell cycle inhibition and pseudo-senescence. (p. 19, l. 1-8)

Further, Applicant's Sequence Listing explicitly sets forth the sequences of twelve Cy motifs.

Applicants respectfully contend that this disclosure fully supports claims 57-60 and 63 as now presented. Embodiments of the invention wherein the expression vector encoded a peptide comprising one or a multiplicity of Cy motif peptides are explicitly disclosed. Applicants respectfully contend that disclosure of alternative combinations of known and disclosed elements is proper support for claims having the asserted scope. Applicants thus respectfully ask the Examiner to withdraw this ground of rejection.

Applicants believe that all grounds of rejection based on 35 U.S.C. §112 have been overcome by amendment or traversed by argument, and respectfully request the Examiner to withdraw these rejections.

CONCLUSION

Applicants believe that the claims fulfill all requirements of patentability, and respectfully solicit their expeditious allowance.

If the Examiner in charge of this application believes it to be helpful, he is invited to contact the undersigned attorney by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

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By: 

Kevin E. Noonan, Ph.D.
Reg. No. 35,303